88-629

No. ———

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

OCTOBER TERM, 1988

UNDETERMINED QUANTITIES OF AN ARTICLE OF DRUG, ANUCORT HEMORRHOIDAL SUPPOSITORIES WITH HYDROCORTISONE ACETATE in any size container in the possession of G & W LABORATORIES, INC., SOUTH PLAINFIELD, NEW JERSEY, Labeled in part: (foil strip) * * * HEMORRHOIDAL-HC SUPP. 0152 * * *

G & W LABORATORIES, INC.,
Petitioner

v.

UNITED STATES OF AMERICA,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

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QUESTION PRESENTED FOR REVIEW

Did the Court of Appeals err in affirming summary judgment that the product Anucort is a "new drug" based upon a reading of *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984), as requiring deference to the Government's novel interpretation of "new drug" under the Federal Food, Drug, and Cosmetic Act where:

(1) Such interpretation was advanced as an agency interpretation for the first time by Government counsel in this litigation and is contrary to regulatory positions taken by the agency in its regulations and in Federal Register Notices concerning closely related drugs before and since this case was instituted.

(2) The Government's interpretation required, as a matter of law, that the courts ignore the uncontroverted opinions of qualified experts that a product is not a new drug under 21 U.S.C. § 321(p) (i.e., that it is generally recognized among experts as safe and effective based on adequate and well-controlled studies), because those expert conclusions were based on studies conducted with similar products which had not been proven to be bioequivalent to the product in question, although FDA had previously accepted similar extrapolations without bioequivalency data.

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G & W LABORATORIES, INC.,
Petitioner

v.

UNITED STATES OF AMERICA,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

The petitioner G & W Laboratories, Inc., respectfully prays that a writ of certiorari issue to review the judgment of the United States Court of Appeals for the Third Circuit entered in this proceeding on August 2, 1988.

OPINIONS BELOW

The decision of the Court of Appeals for the Third Circuit appears as Appendix A. This decision affirmed without opinion the judgment of the United States District Court for the District of New Jersey in *United*

States v. Undetermined Quantities of an Article of Drug . . ., No. 85-523 (August 24, 1987). This decision appears as Appendix B.

JURISDICTION

The decision of the Court of Appeals was entered on August 2, 1988. The Court of Appeals' denial of the Petition for Panel Rehearing was entered on September 7, 1988 (Appendix C). This petition was filed within 90 days of the denial of rehearing under 28 U.S.C. § 2101 (c) and Rule 20.4 of the Rules of the Supreme Court of the United States. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTES INVOLVED

Because of the length of the statutory and regulatory provisions involved, the relevant portions of 21 U.S.C. § 321(p), 21 U.S.C. § 355(d), 21 C.F.R. § 320.22, and 53 Fed. Reg. 30756 (August 15, 1988), are set out as Appendices D, E, F, and G, respectively.

STATEMENT OF THE CASE

This case involves a controversy over the legal status under the Federal Food, Drug, and Cosmetic Act ("the Act") of Anucort Hemorrhoidal Suppositories ("Anucort"), a prescription drug manufactured by Petitioner G & W Laboratories, Inc. ("G & W"). Anucort is a suppository containing hydrocortisone acetate which is intended for intrarectal insertion to provide topical medication to relieve various local inflammatory conditions such as hemorrhoids. This product has been marketed by G & W since approximately 1958.

Respondent, the United States of America ("the Government"), on November 4, 1985, instituted an *in rem* seizure action against a quantity of Anucort on the grounds that it is a "new drug" for which no new drug

application has been approved. Jurisdiction in the District Court for the District of New Jersey was invoked under 28 U.S.C. §§ 1331, 1345 and 21 U.S.C. § 334. G & W, Petitioner herein, filed a claim as the owner of the seized articles of drug and filed an Answer to the Complaint, along with a Jury Demand, on December 19, 1985.

The precise issue in the case below was whether Anucort is a "new drug" as defined in 21 U.S.C. § 321(p). G & W's principal defense was that Anucort is not within the definition of "new drug" because it is, as required by section 321(p),

> . . . generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling.

Applicable case law, including Supreme Court case law, has established that such general recognition must generally be based on "substantial evidence" which is defined in 21 U.S.C. § 355(d), as including adequate and well-controlled clinical trials. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 618; 629-30 (1973).[1]

The Government's Summary Judgment Motion was limited to the issue of whether Anucort is generally recognized as effective among qualified experts (safety is not in question), in accordance with 21 U.S.C. § 321(p) as

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[1] This standard applies unless the drug is one for which a finding of efficacy "might be made without [this] kind of scientific support . . ." *See* Weinberger v. Bentex Pharmaceuticals, Inc., 412 U.S. 645, 652 (1973). G & W has also argued that Anucort is such a drug because of its "longstanding market acceptance . . . so that the body of experience alone, without controlled research could support a finding of general recognition." *See* United States v. Articles of Drug . . . Promise Toothpaste, 629 F. Supp. 776 (N.D. Ill. 1984), *aff'd* 826 F.2d 564 (6th Cir. 1987).

interpreted by this Court in *Hynson, Westcott & Dunning*. G & W submitted affidavits of five highly qualified expert physicians which met the requirement of the *Hynson* rule in that they found Anucort generally recognized as safe and effective for its labeled indications based upon specifically identified adequate and well-controlled studies. *See* Joint Appendix on Appeal to the Third Circuit ("J. A."), pp. 39-129. The Government, however, took the novel position that as a matter of law "substantial evidence" for Anucort could only be based on studies with the exact dosage form of the drug involved, i.e., Anucort itself, or on studies with drugs to which Anucort has been shown to be bioequivalent in published studies. The Government relied solely on one supporting affidavit, attesting only to a literature search which revealed no published adequate and well-controlled studies or bioavailability studies conducted with the Anucort product. As stated by the district court, "[b]ioequivalent drugs have similar 'bioavailability,' meaning that the active ingredients in the drugs are absorbed from the drug product at a similar rate and to a similar extent." (*See* Appendix ("App.") 9a, *citing* 21 C.F.R. § 320.1(a), (e).) The affidavit relied on by the Government did not directly address the question of whether Anucort is generally recognized as safe and effective among experts.

The expert affidavits submitted by G & W each attested to the fact that adequate and well-controlled studies with other similar topically applied steroid products (containing hydrocortisone acetate or similar steroids) can be scientifically relied upon to establish the effectiveness of Anucort suppositories without reference to data showing Anucort to be bioequivalent to the other studied drugs.

G & W's experts stated that because of a number of scientific facts applicable to Anucort (and other essentially identical anti-inflammatory drug products), expert recognition of safety and efficacy can and does exist even though there are no published studies specifically with

this product.[2] The experts also cited various statements and rulings of the federal Food and Drug Administration ("FDA") which demonstrate that FDA has itself extrapolated scientific data from one topically-applied steroid product to another in order to find safety and effectiveness without a bioequivalency showing.[3] G & W had sought to discover further evidence of such FDA actions under Fed. R. Civ. P. 56(f), but its requests for such discovery were denied by the U.S. Magistrate.

The district court filed an opinion granting summary judgment on August 24, 1987. The court held that it was required, under *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), to accept the Government's arguments regarding the exact form of evidence (bioequivalency) needed for general recognition of Anucort's efficacy. Specifically, the court deferred to the Government's position on the issues of (1) the need, as a matter of law, for bioavailability studies to establish the general recognition of any product relying on studies with other products; and (2) whether Anucort is a "top-

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[2] The factors relied upon include the fact that hydrocortisone (including hydrocortisone acetate) was the first of a series of effective anti-inflammatory corticosteroid drugs whose activity is well known in the scientific community; the fact that the quantitative effects of topical corticosteroid drugs are well-known and essentially identical; the fact that a large body of medical literature has established that these drugs are effective in treating topical conditions involving a corticosteroid-responsive inflammatory component; the fact that the conditions for which Anucort is recommended include a corticosteroid-responsive component; and the fact that Anucort and drugs of compositions essentially identical to Anucort have been marketed for many years and are well recognized as safe and effective in the medical community. (J.A. 39-129.)

[3] FDA has, for example, formally adopted the position that in vivo bioavailability studies are not necessary for extrapolation of results for a "topically applied preparation." 21 C.F.R. §§ 320.22(a), (b)(2) (App. 27a-28a). *See* I.A. and I.B. *infra* for other examples.

ical" product and thus covered by the principles of FDA's regulation waiving the need for *in vivo* bioavailability studies to show equivalency, 21 C.F.R. § 320.22(b)(2). The fact that highly qualified experts can and did conclude, on the basis of published adequate and well-controlled studies with identical or closely related active ingredients, that Anucort is generally recognized as safe and effective was dismissed by the court as not complying with the Government's interpretation of the nature and form of the studies legally required. Further, the district court dismissed evidence of FDA's prior actions inconsistent with the Government's litigating arguments on both of these issues as mere "transgressions," and upheld the denial of discovery to obtain further evidence to show that deference to the FDA's interpretations of the law on these issues was inappropriate under the *Chevron* case. (App. 13a.)

G & W timely filed a Notice of Appeal to the United States Court of Appeals for the Third Circuit. On August 2, 1988, the Third Circuit affirmed, without opinion, the district court's decision. (App. 2a.)

Subsequent to the Third Circuit's affirmance, FDA issued on August 15, 1988, a Federal Register Notice, 53 Fed. Reg. 30756, in which it stated conclusions factually inconsistent with the legal positions argued by the Government and accepted by the courts below. This Notice casts further significant doubt on the deference to be afforded the Government's litigating "interpretations" of the law in this case. G & W filed a Petition for Panel Rehearing based on this Federal Register Notice, and simultaneously filed for a stay on the mandate pending this petition for writ of certiorari. Petition for Rehearing was denied on September 7, 1988, and issuance of certified judgment in lieu of formal mandate was stayed until October 14, 1988.

REASONS FOR GRANTING THE WRIT

The affirmance by the Third Circuit Court of Appeals of the district court's opinion raises significant questions of federal law as to the proper application of *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984). The decision below requires deference to positions taken in litigation by Government counsel which do not represent the agency's established position, contrary to *Church of Scientology v. Internal Revenue Service*, 792 F.2d 153 (D.C. Cir. 1986) (opinion of Scalia, J.), and also confers deference on factual as well as legal issues, subverting the normal due process protection which this Court affords those against whom summary judgment is sought. Determination by this Court of the proper application of *Chevron* in this case will affect innumerable potential litigants and enforcement actions involving federal agencies.

The affirmance by the Third Circuit Court of Appeals of the district court's opinion represents the first time that a Court of Appeals has ruled that as a matter of law, and in all cases, "substantial evidence" requires either studies with the product itself, or bioequivalency data (showing the tested drug to be bioequivalent to the product in question) in order to support general recognition of efficacy of drug products under 21 U.S.C. § 321(p). Such interpretation departs from established precedent which has treated this issue as a triable fact question, rather than one for determination by a court on summary judgment.

Resolution of the issues raised by this decision are important questions of federal law, not resolved by this Court, which will affect manufacturers of all drugs not now the subject of a new drug application ("NDA") or an abbreviated new drug application ("ANDA") filed pursuant to 21 U.S.C. § 355, as well as future administration of the Federal Food, Drug, and Cosmetic Act ("Act") in regulating all such drugs and enforcing the provisions of the Act. One of the FDA's

principal enforcement activities is the identification of all drugs on the market not covered by an NDA or an ANDA for potential enforcement action. FDA has recently identified some 5,000 unapproved marketed prescription drug products potentially within this category.[4]

I. Erroneous Deference to the Government Unduly Broadens the Principles of Judicial Deference Established by This Court.

The opinion below[5] relies virtually exclusively on the doctrine of *Chevron U.S.A. Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984), in which this Court required judicial deference to legal interpretations made by administrative agencies. The lower court's reliance on this doctrine was misplaced for several reasons, and must be reversed to avoid future erroneous applications of *Chevron*.

A. Deference Cannot Apply Where Counsel's Interpretation is Contrary to Prior Agency Conduct.

In this case, the court deferred to the Government's positions on (1) the need for bioavailability studies to establish Anucort's general recognition, and (2) whether Anucort is a "topically applied preparation" and thus entitled to waiver of the *in vivo* bioavailability require-

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[4] *See* House Comm. on Government Operations, *Deficiencies in FDA's Regulation of the Marketing of Unapproved New Drugs: The Case of E-Ferol*, H.R. Doc. No. 98-1168, 98th Cong., 2d Sess. 17 (1984). This House investigation of FDA also cited data indicating that the number of unapproved drugs entering the market has been increasing dramatically over the years. *Id.* at 19.

"Unapproved" is not, of course, equivalent to illegal. Approval is necessary only if a product is a "new drug." This case has important implications for establishing when unapproved drugs are or are not "new drugs" as a matter of law.

[5] Since the Court of Appeals affirmed the district court without opinion, references to the opinion below are necessarily to the district court (App. B).

ment under 21 C.F.R. § 320.22(b)(2). (App. 9a-10a, 11a.)

Application of the *Chevron* doctrine was not proper in this case because the "agency" interpretations relied on by the district court were merely positions taken by the Government counsel for purposes of this litigation. They are not the kind of formal agency interpretations entitled to deference under *Chevron.* As stated in *Church of Scientology of California v. Internal Revenue Service,* 792 F.2d 153, 165 (D.C. Cir. 1986):

> The precept that the agency's rationale must be stated by the agency itself stems from proper respect for the branches of government . . . if courts were to accept an agency counsel's position, they would in effect substitute a judicial interpretation for the agency's.

This in fact is what has occurred in this case, in which Government counsel has taken a novel position for purposes of litigation involving a particular drug, and the district court has granted summary judgment simply in deference to that position, creating a legal precedent where no support for it exists.

Not only did the district court defer to positions adopted for the first time during the course of this litigation, but more importantly, it ignored or dismissed contrary agency interpretations issued with greater formality and authority, in direct contradiction to the *Church of Scientology* opinion:

> Even granting [the principle of deference in *Chevron U.S.A. v. Natural Resources Defense Council,* 467 U.S. 837 (1984)], however, it cannot possibly have application where counsel's interpretation in fact does *not* explain agency action but is, to the contrary, incompatible with the agency's settled course of conduct.

Id. at 162 n.4. This is precisely the situation here, where the Government's only prior pronouncements on the dis-

puted issue were inconsistent with the position it adopted for this litigation.

There were at least two FDA rulings prior to this litigation that bioequivalence studies are not necessarily (i.e., as a matter of law) required to demonstrate effectiveness for drugs similar to Anucort when extrapolating from studies of other drugs. First, FDA's regulations on bioavailability and bioequivalence explicitly exempt certain classes of drugs from the general requirement of demonstrating *in vivo* bioavailability before new drug approval, stating that such evidence is "self-evident or not necessary" for a number of classes of drugs. *See* 21 C.F.R. § 320.22(b)(2). "Topically applied preparations" intended for local therapeutic effect, which is how G & W's experts have categorized Anucort, are one of the classes exempted from bioequivalence requirements. The Government has offered no facts contrary to this classification. It simply relies on the statement in its legal memoranda that FDA does not consider Anucort to be a topical drug. The lower court adopted this factually unsupported position as an agency interpretation and refused to accept the cited regulation as relevant. (App. 11a-12a.)

A second prior FDA ruling relevant to the issue of bioequivalence and ignored by the district court is a Federal Register Notice, 49 Fed. Reg. 11888 (March 28, 1984). (J.A. 139.) This notice explicitly recognizes that it is appropriate to find effectiveness of topical corticosteroids by extrapolating from studies of other corticosteroids. Dr. Harry P. Meyer, Jr., Director of FDA Center for Drugs and Biologics, stated:

> The Director has determined that this finding of effectiveness should not be limited to neomycin in combination with one specific corticosteroid because there is no corticosteroid that is unique with respect to therapeutic and toxic affects. [Citations omitted].

> Therefore, the Director considers the two adequate and well-controlled studies that were submitted in support of the neomycin/fluocinolone combination to provide substantial evidence of effectiveness for the other products listed above, each of which is an ointment, cream, or lotion that contains neomycin with an effective corticosteroid.

The Notice goes on to state that pursuant to 21 C.F.R. § 320.22, bioavailability studies are waived as to applications for approval of these topical preparations.

This ruling by FDA (that evidence of bioavailability is unnecessary for extrapolations by experts between topical corticosteroid drugs) directly contradicts the district court's acceptance of the Government's litigating position that bioequivalency studies are required as a matter of law to extrapolate the results of studies of one drug to another drug. If, as this Court has stated in *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629-30 (1973), general recognition of effectiveness must ordinarily be based on "substantial evidence," the standard of effectiveness which is applied for approval of new drugs by FDA, then the standard articulated by the FDA in the 1984 Notice should apply to the general recognition of Anucort. At a minimum, the scientific principles stated in that Notice, interpreted in the light most favorable to G & W, establish a factual issue as to whether bioequivalency studies are required for such products.[6]

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[6] In fact, the district court acknowledged FDA's own prior inconsistent actions concerning extrapolation of data, but dismissed such actions as "transgressions" (App. 13a). However, there can only be one standard for substantial evidence which exists "as a matter of law." Where qualified experts agree on the appropriateness of studies "on the basis of which" they may base their conclusions of general recognition of safety and effectiveness, the substantial evidence standard has been met for the purposes of precluding summary judgment. *See* 21 U.S.C. § 355(d).

B. Subsequent FDA Action Relevant to this Case Also Demonstrates that Deference as Applied Below Was Improper.

On August 15, 1988, a Notice of Proposed Rulemaking ("Notice") was published in the Federal Register (53 Fed. Reg. 30756), in the form of a Tentative Final Monograph on Anorectal Drug Products for Over-the-Counter Human Use. The Notice was signed by the Commissioner of Food and Drugs on behalf of the agency. The Commissioner, in a lengthy narrative preamble to the proposed regulations, sets out FDA's position with respect to the law and facts relating to anorectal drug products and listed certain products which FDA accepts as "not new drugs."

In this Notice, FDA made statements which materially contradict the Government's scientific and legal positions adopted by the district court below and affirmed by the Third Circuit. For example, the Government argued at both the district court and appellate levels that anorectal products such as Anucort must, as a matter of law, be shown to be bioequivalent to other anorectal products before general recognition can be based on studies with those products. Thus, on page 17 of its appellate brief ("Gov. Br."), the Government argued:

> Under the rule of [*Hynson, Westcott & Dunning*, 42 U.S. 609] there can, accordingly, be no general recognition of Anucort in the absence of adequate and well-controlled clinical studies on Anucort or, at a minimum, information required in § 355 to show pharmaceutical equivalence and bioequivalence with another product for which there are adequate and well-controlled clinical studies.

The district court opinion had accepted this position on the theory that it was required to defer to FDA's "interpretation:"

> Section 355(d), defining "substantial evidence," does not directly address whether the necessary studies

> must be of the drug product itself. The language employed—". . . investigations . . . on the basis of which it could fairly and reasonably be concluded by such experts that the drug will [be effective]"—is consistent with either party's interpretation. Under such circumstances, *Chevron* dictates that this court accept FDA's interpretation of § 355(d).

(App. 7a.) However, the August 15, 1988 Federal Register Notice states that:

> . . . With regard to the products subject to this monograph, *FDA will not require in vivo bioavailability testing*, but will address product bioavailability in the context of the monograph requirements of (1) appropriate vehicles and other inactive ingredients, and (2) compliance with appropriate good manufacturing practices.
>
> Accordingly, the agency will not require final formulation testing of anorectal drug products covered by a final monograph. Category I anorectal active ingredients may be formulated in appropriate vehicles without additional testing, provided the product is manufactured according to the regulations for the Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211).

53 Fed. Reg. at 30776 (emphasis added). (App. 29a.)

It should be emphasized that FDA is listing these anorectal products as "not new drugs" and permitting their marketing without the submission of *any* bioequivalency or other data. Only if certain requirements dealing with formulations and/or manufacturing procedures are not met will FDA take action. It is clear that under this Notice, no bioavailability "studies" are required, and only good manufacturing practices and appropriate inactive ingredients are needed to avoid new drug status.

Similarly, the Government argued on pages 18-22 of its appellate brief that Section 320.22(b)(2) of its regu-

lations, exempting topical products from bioavailability requirements, does not apply to Anucort because Anucort is not a "topically applied preparation, e.g., a cream, ointment or gel, intended for local therapeutic effect" under the terms of this regulation:

> FDA interprets this provision to apply only to drugs that are applied directly to the site of drug action indicated in the labeling. As it is undisputed that Anucort is a rectal suppository indicated for the treatment of anal conditions, which are outside the rectum, it is not "topically applied . . . for local therapeutic effect" under FDA's interpretation of the regulation, which must be accorded deference. . .

(Gov. Br. at 21-22.)[7] The district court again simply held that it "must defer to FDA's reasonable interpretation of its own regulations," and concluded as a matter of law that Anucort was not exempt under § 320.22 as a topical product. (App. 11a.) However, FDA in the August 15, 1988 Federal Register Notice states specifically that:

> . . . FDA agrees with the comment that final formulation testing should not be required for anorectal drug products *because the products are topically applied* and because, to date, there has been no demon-

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[7] After the district court judgment but prior to affirmance by the Third Circuit, G & W obtained (through the Freedom of Information Act) a ruling by the FDA's Division of Bioequivalence in connection with the approval of an application for an abbreviated new drug approval (ANDA) of an aerosol drug intended for intrarectal administration for the treatment of anal conditions. This product is similar to Anucort in that both are drugs containing hydrocortisone which are intended to be administered intrarectally for treatment of anal inflammatory conditions. This ruling directly contradicts the Government position in this case by stating that such a product is a "topically applied preparation intended for local therapeutic effect," and is therefore deemed bioequivalent to the existing rectal product under 21 C.F.R. § 320.22(b)(2). *See* letter from G & W counsel to Third Circuit Clerk (June 29, 1988) and response by Government counsel (July 8, 1988).

> strated bioavailability problem with any of the products at issue. The in vivo waiver provision of § 320.22(b)(2) for topically applied products reflects the fact that certain topically applied products, that are applied directly to the site of drug action, are less prone to bioavailability problems than are some other drugs and, accordingly, their bioavailability may, in some instances be determined by means other than in vivo product testing. . .

(App. 29a) (emphasis added).

This Notice by its terms applies to anorectal suppositories for intrarectal use, which are specifically referenced in the proposed regulations (*see, e.g.*, proposed § 346.50 (Labeling of anorectal drug products), 53 Fed. Reg. at 30784, ". . . (4) For products for intrarectal use that are wrapped suppositories . . .") Thus, FDA's own very recent application of § 320.22(b)(2) permits rectal suppositories to be declared "not new drugs" without bioavailability studies.

The August 15, 1988 Notice demonstrates that FDA does in fact and in law accept the scientific reasoning urged by G & W and its expert affiants, despite the assertions of Government counsel to the contrary. Further, the Notice also demonstrates the validity of G & W's request for discovery to show that the Government's "legal" arguments are contrary to factual positions which FDA has taken in the past, and which it continues to take in essentially identical situations. This case thus presents precisely the dangers of the *Chevron* doctrine envisioned by *Church of Scientology v. Internal Revenue Service*, 792 F.2d 153, 165 (D.C. Cir. 1986).[8]

Because the district court did not have an opportunity to review this Notice, in which FDA directly contradicts Government positions taken in this case, G & W submits that this Court's power of review should be exercised to

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[8] *See* discussion *supra*, p. 9.

correct the misapplication of *Chevron* in giving deference to legal arguments which misrepresent actual agency practice. The results of this case also represent an opportunity for this Court to define more clearly and to restrict appropriately the application of deference to federal agency interpretations under *Chevron*.

C. The Chevron Doctrine Does Not Apply to Factual Determinations.

The *Chevron* doctrine by its terms applies to legal interpretation and not to factual determinations:

> If Congress has explicitly left a gap [in administering a congressionally created program] for the agency to fill, there is an express delegation of authority to the agency to elucidate a specific provision of the statute by regulation . . . In such a case, the court may not substitute its own construction of a statutory provision for a reasonable interpretation made by the administrator of an agency.
>
> We have long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer . . .

Chevron at 843-44. In the *Chevron* case, this Court permitted the Environmental Protection Agency to provide its own construction of the congressional "gap" leaving open the precise definition of the term "stationary source" in the Clean Air Act Amendments. (*See Chevron*, 476 U.S. at 843-44.) Subsequent cases applying *Chevron* clearly involve not factual issues but legal interpretations of statutory provisions. *See, e.g., Young v. Community Nutrition Institute*, 476 U.S. 984 (1986) (addressing the question of whether the words "to such extent" in 21 U.S.C. § 346 modify "shall" or the phrase "the quantity therein or thereon").

By contrast, the questions as to which the district court opinion invoked the doctrine in this case were sin-

gularly factual in nature. Specifically, the court deferred to the Government's position on (1) the need for bioavailability studies to establish Anucort's "general recognition" of effectiveness among experts, and (2) whether Anucort is a "topically applied preparation" and thus entitled to waiver of the *in vivo* bioavailability requirement under 21 C.F.R. § 320.22(b)(2). These questions became legal issues only because the Government provided no factual support in the record for its positions, and was unable to counter the factual conclusions presented by G & W experts.

"General recognition" of effectiveness of a drug must be based upon "substantial evidence" as defined in the Act. Substantial evidence is defined in 21 U.S.C. § 355(d) as:

> . . . evidence consisting of adequate and well controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

As is clear from the language of this section, the question of whether particular studies are sufficient to prove effectiveness, i.e., to constitute "substantial evidence," is uniquely dependent upon whether qualified experts can decide that the studies in question are sufficient to support a conclusion of effectiveness.

The district court described the language in section 355(d) as "consistent" with its conclusion that bioequivalency studies are required as a matter of law before data can be extrapolated from a study of one drug product with the same active ingredient to support general recognition of another with the same active ingre-

dient. (App. 7a.) However, there is nothing in the statute to support the district court decision. The statute by its terms requires only such adequate and well-controlled studies as are necessary to support a fair and responsible expert conclusion. The exact nature of such studies is clearly a factual question for determination by scientific and medical experts, not a question of law for attorneys or judges. Whether or not bioavailability or bioequivalency studies are required depends on whether such studies are needed for experts to draw conclusions as to the effectiveness of the particular drug involved.

With respect to its conclusion that Anucort is not a 'topical preparation" covered by 21 C.F.R. § 320.22(b)(2), the district court stated:

> The Government contends that suppositories are not "topically applied preparations"; G & W's experts disagree. Interpretation of this regulation, however, is a matter of law and the court must defer to FDA's reasonable interpretation of its own regulation.

(App. 11a.)[9] Although the court attempted to frame the issue as if it were merely one of statutory interpretation, whether a drug is topical is inherently a factual issue, and deference to FDA was not appropriate in this context. The mere fact that the application of a regulation is involved does not bring an issue within the *Chevron* doctrine. Scientific principles and expert opinion are essential to the determination of "substantial evidence" for purposes of general recognition under 21 U.S.C. § 321(p) and in determining the meaning of "topically applied preparation," and cannot be overridden simply by invoking *Chevron*.

Judicial deference as applied by *Chevron* is appropriate only in the context of judicial review of actions

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[9] The court's decision relating to the need for bioequivalency studies was also specifically based on *Chevron*. (App. 7a, quoted *supra*, pp. 12-13.)

based on an agency's construction of an ambiguous statute. To apply the same deference mandated by that context to factual issues in an enforcement action against the claimant's product, where there has been no administrative determination and where the Government is required under the Act to shoulder the burden of proof, contradicts the most basic due process rights to be accorded a summary judgment opponent.

II. The Decision Below Conflicts with Prior Judicial Applications of 21 U.S.C. § 321(p) and § 355(d).

The district court cited *Premo Pharmaceutical Laboratories v. United States*, 629 F.2d 795 (2d Cir. 1980) in support of its conclusion that bioequivalency studies are always required before data can be extrapolated from one drug product to support the safety and efficacy of another. (App. 8a.) This is a misstatement of the principles applied in *Premo*, and, in fact, conflicts with the legal principles of general recognition applied by the Second Circuit in that case. In *Premo*, there was uncontroverted evidence that differences between the orally administered product in question and the similar product relied upon were such that they might affect safety or efficacy. There was, in fact, an extended trial on the merits involving, inter alia, the adequacy of unpublished bioequivalence data. The Second Circuit based its conclusion of "new drug" status on the existence of a factual showing; namely, ". . . for the undisputed reason that a difference of inactive ingredients, as exists here, when combined with the active ingredient, can affect the safety and effectiveness of the drug product . . ." 629 F.2d at 805.

Thus, contrary to the district court's ruling below, *Premo* does not hold that extrapolation from a study of one drug to another without a bioequivalency study is insufficient as a matter of law on the issue of general recognition. *Premo* does, however, hold that it is inap-

propriate for a Court to weigh the scientific evidence and make its own determination of safety and efficacy. *Id.* This is in essence what the courts below in this case have done by accepting, on summary judgment, the Government's position on the type of scientific evidence required for general recognition of effectiveness, rejecting all of G & W's expert opinions directly contradicting that position.

Other precedents cited by the district court are equally inappropriate since, in each case where products were held to be "new drugs" because of possible bioavailability problems, there was factual evidence that extrapolation from one drug to another would not be appropriate because of the actual differences between the products sought to be compared.[10] In each case, the question was decided as a mater of fact. Thus, for example, in *United States v. Undetermined Quantities of Various Articles of Drugs*, 675 F.2d 994, 1001 (8th Cir. 1982), the court relied on the testimony of a Government witness regarding the need for bioavailability studies as applied to the type of drug product in question, and the district court's findings of fact were sustained only after review of the testimony.

In this case, the courts below failed to apprehend that cases which have held that the products involved were not generally recognized as safe and effective because of possible bioavailability differences do not support a requirement for bioavailability studies as a matter of law, in all cases. This distinction, between finding that bio-

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[10] The case of United States v. Atropine Sulfate 1.0 MG (Article of Drug) . . . Dey-Dose, 843 F.2d 860 (5th Cir. 1988), decided after the district court opinion in this case, upheld a summary judgment decision that the product involved was a "new drug" which could not rely on studies with other products for "general recognition of effectiveness." That decision was, however, based on the fact that no products containing atropine as an active ingredient had ever been approved by FDA. That is not an issue in this case.

equivalency studies are required as a matter of fact, and a legal holding that such bioequivalency studies are always necessary, is an important question of federal law which requires authoritative review by this Court.

III. The Decision Below Requires That the Issue Left Open by This Court in *United States v. Generix Drug Corp.* Now Be Resolved.

The decision of the courts below, purporting to establish the need for bioequivalency studies as a legal requirement before experts can form an opinion on general recognition, presents the issue left unresolved by this Court in *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983), *rev'g* 654 F.2d 1114 (5th Cir. 1981). In the original district court case on review in that case, *United States v. Generix Drug Corp.*, 498 F. Supp. 288 (S.D. Fla. 1980), the Government failed to make a factual showing of the need for bioequivalency studies for two of the eight drug products involved. For the other six drugs in question in that case, the Government did show that there was "some reasonable possibility that differences between the copied drug product and the generic drug product affect the safety and effectiveness of the generic drug product," and on this basis, further distribution of these six products was enjoined. *Id.* at 293-94. For the two drugs for which there was no such showing, the district court denied the injunction sought by the Government.

The defendants appealed the district court injunction affecting its six drugs, but the Government did not cross-appeal as to the other two. The Fifth Circuit reversed the lower court ruling, but was in turn reversed by this Court. In its opinion, this Court specifically noted that since the Government had not appealed the district court's refusal to grant relief as to the other two products, it "had no occasion to pass on" the district court's conclusion that FDA has the burden of showing a "reasonable possibility" that a drug product is not bioequiv-

alent to an approved product in order to have a court enjoin distribution based on alleged "new drug" status. *See* 460 U.S. at 461 n.12.

The unappealed requirement formulated by the district court in *Generix*—that there must be "some reasonable possibility" that the differences between the tested drug and the drug for which "general recognition" is sought will affect safety and effectiveness—is clearly a factual issue and cannot be determined as a matter of law on summary judgment. The district court in this case cited *Generix* for the proposition that "drug" as used in Sections 321(p) and 355(d) refers to the product itself, and not simply the product's active ingredients. (App. 7a.) However, the district court failed to recognize that the lower court in *Generix* treated the issue of the requirement of bioequivalency studies as a fact question, and that this Court had left open the issue of whether the Government must make a showing that different drugs are not bioequivalent before bioequivalency studies are required for a showing of general recognition.[11] If the portion of the district court decision in *Generix* which was left undisturbed by this Court had been applied to this case, summary judgment could not have been granted because of the Government's failure to make any showing of a reasonable possibility of lack of bioequivalence with respect to Anucort.

Resolution of this issue is essential to all future litigation under the Act involving the issue of whether experts may rely on studies with similar or even identical products, even when those studies are in fact "adequate and

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[11] This "open issue" was recently discussed by the Fifth Circuit in United States v. Atropine Sulfate 1.0 MG. (Article of Drug) . . . Dey-Dose, 843 F.2d 860 (5th Cir. 1988) (*see* note 10 *supra*). While noting that the Supreme Court in *Generix* did not decide whether there must be a "reasonable possibility" that products are not equivalent before bioavailability studies are required, the *Dey* decision also failed to answer this question.

well-controlled studies" which establish effectiveness in accordance with 21 U.S.C. §§ 321(p), 355(d), and *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609 (1973). If there must be a showing of "some reasonable possibility" that the difference between drugs will affect safety and effectiveness, then the decision below must be reversed. To reverse and require a positive showing by the Government would be consistent not only with prior judicial interpretations of "substantial evidence" as a fact issue, but would reconcile this case with settled principles of summary judgment established by this Court. As the movant for summary judgment, the Government in this case had the clear burden of identifying specifically the materials that demonstrated the absence of any genuine issue of material fact. *Celotex Corp. v. Catrett*, 477 U.S. 317, 106 S. Ct. 2548, 2554 (1986). Without any positive showing of need for bioavailability studies, and in direct contradiction to the expert testimony offered by G & W, the granting of summary judgment in favor of the Government was inappropriate and denied G & W its right to be fairly and fully heard at trial.

CONCLUSION

For the foregoing reasons, the Petitioner, G & W Laboratories, prays that this Honorable Court grant the instant Petition for Writ of Certiorari and, upon review, reverse the decision of the Third Circuit Court of Appeals, and of the District Court for the District of New Jersey, in holding Anucort to be a "new drug" within the meaning of 21 U.S.C. § 321(p) for purposes of summary judgment, and that the case be remanded to the district court for full discovery and trial on the merits.

Respectfully submitted,

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October 14, 1988

APPENDICES

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 88-5030

UNITED STATES OF AMERICA

v.

UNDETERMINED QUANTITIES OF A DRUG, ANUCORT HC SUPPOSITORIES CONTAINING HYDROCORTISONE ACETATE in any size container in the possession of G&W LABORATORIES, INC., SOUTH PLAINFIELD, NEW JERSEY, labeled in part: (foil strip) "* * * HEMORRHOIDAL-HC SUPP. 0152 * * *"

G & W LABORATORIES, INC., CLAIMANT,
Appellant

Appeal from the United States District Court
for the District of New Jersey (Newark)
(D.C. Civil Action No. 85-5232)
Dist. Judge: Hon. H. Lee Sarakin

Argued July 27, 1988

Before: HIGGINBOTHAM, BECKER and GREENBERG, *Circuit Judges.*

JUDGMENT ORDER

After consideration of all contentions raised by appellant, it is

ADJUDGED AND ORDERED that the judgment of the district court be and is hereby AFFIRMED.

Costs taxed against appellant.

BY THE COURT

/s/ A. Leon Higginbotham
Circuit Judge

Attest:

/s/ Sally Mrvos
SALLY MRVOS
Clerk

Aug. 2, 1988

APPENDIX B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civil Action No. 85-5232

UNITED STATES OF AMERICA,
Plaintiff,

v.

UNDETERMINED QUANTITIES OF AN ARTICLE OF DRUG, . . .
(ANUCORT HC SUPPOSITORIES),
Defendants.

[Filed Aug. 24, 1987]

SAROKIN, District Judge.

OPINION

In this action for seizure and condemnation of a drug, the United States moves for summary judgment.

BACKGROUND

"Anucort Hemorrhoidal Suppositories with Hydrocortisone Acetate" (Anucort) is a prescription drug sold to the public for use in treatment of hemorrhoids. G & W Laboratories, claimant herein, began marketing a drug under this label in 1980.

On November 7, 1985, the United States seized an undetermined quantity of Anucort, pursuant to a complaint of forfeiture. The government's amended complaint, filed November 14, 1985, seeks condemnation of

the seized drug on two grounds. First, the government alleges that Anucort is a new drug, as defined by relevant federal statute, that has not been approved by the Federal Drug Administration (FDA). Second, the government alleges that Anucort is a prescription drug under the statute that has been misbranded.

G & W's answer contains several defenses. First, G & W contends that Anucort is not a new drug and therefore not subject to the required FDA approvals. Second, G & W claims that Anucort is exempted from the new drug approval scheme because it was commercially used and sold prior to the statute's enactment date. Third, G & W contends that the court must remand the matter to the FDA for an initial administrative hearing concerning Anucort's status as a new drug. Fourth, G & W argues that FDA's internal enforcement guidelines preclude this action.

On June 11, 1986, the government moved for summary judgment. The government also moved before the Hon. Ronald J. Hedges, U.S. Magistrate, for a stay of discovery pending resolution of the summary judgment motion. G & W cross-moved for a continuance of the summary judgment motion pending further discovery. On October 16, 1986, Magistrate Hedges granted the government's motion for a stay of discovery and denied G & W's motion for a continuance.

G & W appealed the Magistrate's order to this court. On November 24, 1987, at a hearing on the motion, the parties agreed to proceed with the summary judgment motion solely on the ground that Anucort is a new drug because there exists no substantial evidence supporting its safety and efficacy.[1]

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[1] Counsel for the FDA described the ground upon which the motion would be based as the "lack of substantial evidence to form a basis for general recognition," or the "first heading" of its memorandum in support. Transcript of Proceedings, November 24, 1986, at 27:4 to 7.

On February 17, 1987, the court entered an order that 1) reserved decision on G & W's appeal; 2) stated that plaintiff's summary judgment motion would be directed only to "whether there is a lack of substantial evidence to support a finding that the seized drug is generally recognized as effective as contained in Plaintiff's brief in support of its Motion for Summary Judgment"; 3) stating that the government may rely on only one affidavit, to be submitted, "addressing the existence of relevant studies"; 4) granting G & W the right to submit an opposing affidavit; 5) granting the parties leave to depose the respective affiants.

On February 11, 1987, the government submitted the affidavit of Dr. C. Carnot Evans. G & W moved to disregard statements in the affidavit, arguing that its contents violated the court's order. The court, by order dated April 20, 1987, reserved decision on G & W's motion pending its ruling on plaintiff's summary judgment motion. The court also granted G & W the right to depose Dr. Evans and two FDA employees who conducted the literature searches mentioned in Dr. Evans' affidavit.

G & W chose to depose only Mr. Kenter, one of the FDA employees. On May 26, 1987, the court granted G & W's motion to require the government to provide G & W with citations of studies referred to in notes prepared by Mr. Kenter.

The court now considers plaintiff's motion for summary judgment, as reshaped by this procedural history.

DISCUSSION

I. *Substantial evidence*

Before the court is the question of "whether there is a lack of substantial evidence to support a finding that the seized drug is generally recognized." Plaintiff, to

prevail on its motion for summary judgment, must demonstrate that no genuine issue of material fact exists with respect to this question.

"Substantial evidence," in this context, means

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d).[2]

At dispute is the nature of the "adequate and well-controlled investigations" required by the above definition. The government contends that § 355(d) requires published studies of the product Anucort itself. G & W contends that studies of other drugs containing the same active ingredient (hydrocortisone acetate) as Anucort constitute substantial evidence under § 355(d).[3]

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[2] Technically, the question before the court is whether Anucort is "generally recognized" as safe and effective by qualified experts, so as to be outside the definition of a "new drug." 21 U.S.C. § 321(p). However, a finding of "general recognition" under § 321(p) must be based on at least "substantial evidence" as defined in § 355(d). *See United States v. Rutherford*, 442 U.S. 544, 549 n. 7 (1978); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 629, 632 (1973).

[3] G & W also contends that Dr. Evans affidavit erroneously states, at ¶ 15, that there are no such studies of "any product with the same formulation of active ingredients as the Anucort product." The government responds that it was aware of these Anusol studies, but that the formulation of the specific Anusol drugs tested is different than that of Anucort. Furthermore, the studies of Anusol-HC do not purport to be adequate and well-controlled. Even accept-

The court, in evaluating the validity of the FDA's interpretation of § 355, must follow the analysis set forth by the Supreme Court in *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). If the statutory provision unambiguously expresses Congress' intent on the precise question at issue, the court and the agency must follow the plain language; however, if the provision is silent or ambiguous as to the relevant issue, the court must defer to the agency's interpretation as long as that interpretation is reasonable. See *id.* at 842-33; *Young v. Community Nutrition Inst.*, 106 S. Ct. 2360, 2364 (1986) (applying *Chevron* to an FDA interpretation of the Food, Drug, and Cosmetic Act).

Section 355(d), defining "substantial evidence," does not directly address whether the necessary studies must be of the drug product itself. The language employed—". . . investigations . . . on the basis of which it could be fairly and reasonably be concluded by such experts that the drug will [be effective]"—is consistent with either party's interpretation. Under such circumstances, *Chevron* dictates that this court accept FDA's interpretation of § 355(d).

Furthermore, such a result is consistent with prior judicial interpretation of the new drug provisions of the Act.

As an initial matter, "drug," as used in § 321(p) and § 355(d), refers to the product itself, and not simply the product's active ingredients. *See United States v. Generix Drug Corp.*, 460 U.S. 453, 456-57 (1983). Two

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ing, however, that a genuine issue exists as to the existence of studies of the same formulation of active ingredients, such an issue is not material given this court's holding that studies of drugs other than Anucort may be substantial evidence of Anucort's effectiveness only if 1) the active ingredients are the same and 2) the drugs are demonstrably bioequivalent. *See infra.*

drugs with the same active ingredients, but different inactive ingredients(excipients), may be released into the body at different rates. See *id.* at 455; *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F. 2d 795, 805 (2d Cir. 1980). For that reason, courts have rejected arguments that studies of approved drugs containing the same active ingredients as a newly marketed product, in and of themselves, constitute substantial evidence that the new product is generally recognized as safe and effective. *See, e.g., United States v. Undetermined Quantities of Various Articles of Drug*, 675 F. 2d 994, 1001-02 (8th Cir. 1982); *Premo Pharmaceutical Laboratories, Inc.*, 629 F. 2d at 805; *United States v. Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 965-973 (D.N.J. 1981); *Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F. Supp. 100, 102-03 (D.N.J. 1979), *aff'd*, 596 F. 2d 568, 570 (3d Cir. 1979).[4]

However, courts have recognized that studies of a "bioequivalent" drug may be used to show safety and effectiveness of a new product. *See United States v. Undetermined Quantities of Various Articles of Drug*, 675 F. 2d 994, 1001-02 (8th Cir. 1982); *United States v. Premo Pharmaceutical Laboratories*, 511 F. Supp. at 985-88; *cf. United States v. Generix Drug Corp.*, 460 U.S. at

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[4] *United States v. Articles of Drug (Lannett)*, 585 F.2d 575 (3d Cir. 1978), cited by G & W, is neither binding nor persuasive authority to the contrary. The Third Circuit, in dictum, supported G & W's position concerning extrapolation of studies. However, two courts within this district have expressly rejected the *Lannett* reasoning as contrary to the Act's intent. *See United States v. Premo Pharmaceutical Laboratories, Inc.*, 511 F. Supp. 958, 973 (D.N.J. 1981); *Pharmadyne Laboratories, Inc. v. Kennedy*, 466 F. Supp. 100, 102-03 (D.N.J.), *aff'd on other grounds*, 596 F. 2d 568, 570 (3d Cir. 1979) (distinguishing, but not expressly rejecting *Lannett*). Furthermore, the Supreme Court's expression that differences in excipients must be considered in evaluating the safety and effectiveness of a new drug, *United States v. Generix Drug Corp.* 460 U.S. 453, 460-61 (1983), is inconsistent with *Lannett*.

461 (not reaching the question of whether two "demonstrably bioequivalent products" might be considered the same "drug"). Bioequivalent drugs have similar "bioavailability," meaning that the active ingredients in the drugs are absorbed from the drug product at a similar rate and to a similar extent. *See* 21 C.F.R. § 320.1(a), (e).

Moreover, a 1984 amendment to the Act introducing a scheme for abbreviated new drug applications (ANDAs) verifies the significance of bioequivalence. 21 U.S.C. § 355(j). Such applications permit approval of new drug products that are closely related to previously approved products. An ANDA will be approved only if it contains "information to show that the new drug is bioequivalent to the [previously approved] drug." 21 U.S.C. § 355(j)(2)(A)(iv). Congress, by establishing an ANDA procedure with a bioequivalence requirement, confirmed that substantial evidence regarding a new product cannot consist merely of studies of a previously approved product containing the same active ingredients.

Neither Congress nor the courts have determined the precise manner by which bioequivalence of two drugs may be established. The government contends first that the Federal Drug Administration (FDA) is the only body capable of properly testing for bioequivalence. *See United States v. Premo Pharmaceutical Corp.*, 511 F. Supp. at 987. Alternatively, the government argues that substantial evidence of bioequivalence must meet the basic statutory definition—that is, adequate and well-controlled, published studies. Given the current record in this matter, the court need not resolve this question. The court holds that bioequivalence must be demonstrated by "substantial evidence" as defined in § 355(d).

Based on the required deference to the FDA's interpretation as well as available precedent, the court holds that, as a matter of law, G & W may satisfy the "sub-

stantial evidence" requirement only by (1) adequate and well-controlled studies of the product Anucort itself or by (2)(a) adequate and well-controlled studies of another drug with the same active ingredients as Anucort and (b) adequate and well-controlled studies demonstrating that the other drug and Anucort are bioequivalent. Dr. Evans' uncontradicted affidavit establishes that G & W can satisfy neither of these requirements. The FDA literature search failed to reveal any published studies of the Anucort product or any studies "relating to the bioavailability of Anucort." ¶ 15. Dr. Evans, based on the results of the literature search and his personal knowledge, opined that no published studies exist of either the Anucort product, ¶ 16, or Anucort's bioavailability, ¶ 17. This affidavit satisfies plaintiff's burden under Rule 56(c) to establish that there exists no genuine issue of material fact and that plaintiff is entitled to judgment as a matter of law. *See Matsushita Electric Inds. v. Zenith Radio Corp.*, 106 S. Ct. 1351, 1356 (1986).[5]

Given this showing by the government, G & W must set forth specific facts showing that a genuine issue exists regarding the substantial evidence question. Fed. R. Civ. P. 56(e); *Matsushita Electric Inds.*, 106 S. Ct. at 1356. The court rejects each of G & W's attempts to raise such an issue.

First, G & W supplies the affidavits of several experts. These affidavits do not contradict Dr. Evans' statements.

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[5] The court denies G & W's motion to strike Dr. Evans' affidavit. The court relies on ¶¶ 15-17, which contain the results of the literature search and the doctor's opinions based on these results that no published studies exist relating to the safety and effectiveness of Anucort itself or to Anucort's bioavailability. Given the court's interpretation of the Act, these statements are not contrary to the court's February 17, 1987 order stating that the affidavit "shall concern the results of a literature search as to whether there are published studies concerning the safety and effectiveness of Anucort."

These experts all state that they consider Anucort to be safe and effective based on published studies showing that hydrocortisone acetate, Anucort's main active ingredient, is safe and effective. See Declaration of Dr. Vincent P. Zarro, ¶¶ 5,6,18; Declaration of Dr. A.W. Martin Marino, ¶¶ 6, 7; Declaration of Dr. Peter J. Wilk, ¶¶ 5,6,7; Declaration of Dr. Steven Z. Brandeis, ¶ 6; Declaration of Dr. Ira Mark Barash, ¶ 7. These experts state also that medical experts have long accepted extrapolation of results from one corticosteriod (the class of active ingredients used in this treatment) to another.

The affidavits do not raise a triable issue of fact regarding the "substantial evidence" question. As stated above, courts have consistently rejected the argument that studies of approved drugs containing the same active ingredients as a newly marketed product, in and of themselves, constitute substantial evidence that the new product is safe and effective. Furthermore, statements that medical experts generally permit extrapolation among active ingredients in this area, even if accepted by the court, do not address the question of bioequivalence, or how the mixture of these ingredients with different excipients affects release of the ingredients into the body.

Second, G & W asserts that a triable issue exists as to whether Anucort is exempted from demonstrating bioequivalence under 21 C.F.R. § 320.22(b)(2). This section waives the requirement for submission of evidence of bioavailability for "a topically applied preparation, e.g., a cream, ointment, or gel, intended for local therapeutic effect." The government contends that suppositories are not "topically applied preparations"; G & W's experts disagree. Interpretation of this regulation, however, is a matter of law, and the court must defer to FDA's reasonable interpretation of its own regulation. *See, e.g., Vineland Chemical Co. v. United States Envtl. Protection Agency*, 810 F. 2d 402, 409 (3d Cir. 1987);

Revak v. National Mines Corp., 808 F. 2d 996, 1002 (3d Cir. 1986). The court concludes, as a matter of law, that Anucort is not exempted from presenting evidence of bioequivalence by 21 C.F.R. § 320.22(b)(2).

Third, G & W attempts to raise a triable issue of fact by maintaining that the FDA "has announced that it is appropriate to extrapolate from studies with one product to demonstrate effectiveness for other similar products." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 14. G & W's argument is premised principally on a March 1984 statement by Harry M. Meyer, Jr., then Director for FDA's Center for Drugs and Biologics. In that statement, dealing with effectiveness of a combination drug containing neomycin as an active ingredient in combination with a corticosteroid similar to that used in Anucort, Meyer stated:

> The Director has determined that this finding of effectiveness should not be limited to neomycin in combination with one specific corticosteriod because there is no corticosteriod that is unique with respect to therapeutic and toxic effects. [Citations omitted.] Therefore, the Director considers the two adequate and well controlled studies that were submitted in support of the neomycin/fluocinolone combination to provide substantial evidence of effectiveness for the other products listed above, each of which is an ointment, cream, or lotion that contains neomycin with an effective corticosteriod.

49 Fed. Reg. 11888, 11889 (1984).

This statement does not raise a triable issue of fact. The statement explains only that corticosteroids, as active ingredients, are equally effective. The statement does not address, however, any questions of bioavailability—that is, how these active ingredients, when mixed with different excipients, are released to the body. Therefore, this FDA statement does not explicitly state that a find-

ing of effectiveness for one drug may be extrapolated to another drug without an analyis of the two drugs bioequivalence.

However, the FDA statement does not indicate that a bioequivalence finding was made in this particular case.[6] Even assuming that FDA did make such a finding in that matter, the law is plain that extrapolation based solely on identical active ingredients is improper—some finding of bioequivalence is required. Given this, FDA's possible transgressions in approving this combination drug are irrelevant to the question of substantial evidence to support a finding of effectiveness of Anucort. Any issue of fact raised by G & W concerning FDA action on the combination drug application is not material to this matter.[7]

G & W, though failing to oppose plaintiff's motion by raising a genuine issue of fact under Rule 56(c), contends also that the court must deny the motion because further discovery is needed. Rule 56(f) permits a party to oppose a summary judgment motion by identifying facts essential to its opposition upon which further discovery is needed.

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[6] The statement indicates that requirements for *in vivo* (in the human body) bioavailability testing were waived by regulation for the drug product at issue. 49 Fed. Reg. at 11890. The government, in their brief, state that "FDA is still required to perform a biopharmaceutical analysis." Memorandum of Law in Reply to Claimant's Response to Motion for Summary Judgment, at 29 n.18. Nowhere does the FDA statement indicate, however, that FDA determined that the two combination products involved in this situation were bioequivalent before FDA permitted the extrapolation of studies.

[7] G & W also points to a January 1982 statement by an associate director at FDA to the effect that studies of effectiveness of a corticosteroid in curing certain conditions will be extrapolated to prove effectiveness in curing other conditions. Such a statement is irrelevant to whether FDA requires substantial evidence of bioequivalence between two different drug products.

G & W states that further discovery is needed to ascertain "evidence of specific instances in which FDA has approved drugs based on extrapolation." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 24. G & W maintains that this information is relevant "depending on how similar the drugs approved by extrapolation are to Anucort." The court rejects G & W's relevance argument. This court has held, as a matter of law, that studies of an approved drug may not be extrapolated to a newly marketed product simply because the new product contains the same active ingredient as the approved drug—some evidence of bioequivalence is required. This principle has been recognized by several courts and is clearly the present position of the FDA. *See, e.g., United States v. 118/100 Tablet Bottles*, No. 86-1353, slip op. at 2,3 (W.D. La. May 18, 1987). G & W could not defeat plaintiff's motion by demonstrating specific instances in the past where FDA may have deviated from the law; as stated above, such past transgressions would not relieve FDA of its statutory duty in this matter.

The court concludes that plaintiff has demonstrated, as a matter of law, that there exists a lack of substantial evidence to support a finding that Anucort is generally recognized as safe and effective.[8] The court further concludes that G & W has not demonstrated a need for further discovery to oppose plaintiff's summary judgment motion on this issue.

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[8] The court, for the same reasons expressed above, rejects G & W's argument that Anucort falls into an exception to the substantial evidence standard enunciated in *Weinberger v. Bentex Pharmaceuticals*, 412 U.S. 645 (1973). G & W's argument in this regard is nothing more than a reformulation of its main argument in a different guise.

The court's holding regarding substantial evidence obviates the need to address plaintiff's argument that Anucort fails to meet the requirements for a "combination drug."

II. *G & W's affirmative defenses*

Plaintiff, to prevail on its motion for summary judgment, must also demonstrate that G & W's affirmative defenses fail as a matter of law.

A. *Grandfather clause*

G & W alleges in its answer that Anucort falls within a 1962 amendment to § 321(p) that provides:

> In the case of any drug, which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by § 201(p) of the basic Act [21 U.S.C. § 321(p)] as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

Pub. L. 87-781, § 107(a)(4) (1962). A drug is exempt from the new drug provisions of the act if four conditions are met: 1) the drug was commercially used or sold in the U.S. prior to October 1962; 2) the drug was not a "new drug" under the pre-amendment Act; 3) the drug was not covered by an effective new drug application prior to October 1962; 4) the drug is currently intended solely for use under conditions prescribed or recommended in its 1962 labeling. *See United States v. Articles of Drug: 5,906 Boxes*, 745 F.2d 105, 108 (1st Cir. 1984), *cert. denied*, 470 U.S. 1004 (1985). This regulatory exemption must be strictly construed, and G & W has the burden of proof as to each condition. See *id.* at 113.

The government may obtain summary judgment dismissing this defense if it can establish that no genuine issue of fact exists for any of the four necessary condi-

tions. The government argues, based on FDA records,[9] that Anucort fails to meet any of the requirements.

G & W responds that the declaration of Carl J. Greenblatt, G & W's founder and chairman of the board, creates a genuine issue of fact that, under Rule 56(c), precludes the grant of summary judgment. The court finds, however, that G & W's grandfather clause fails as a matter of law even upon crediting Mr. Greenblatt's declaration.

The grandfather clause requires that the "drug" must have been commercially sold or used in the United States prior to 1962. Mr. Greenblatt's statement concerning this requirement is as follows:

> Ever since its introduction in 1958-59, G & W has regularly manufactured and distributed an Anusol-HC formula suppository. Originally these drugs were labeled simply as "hemorrhoidal suppositories with hydrocortisone acetate." However, since 1980-81, *the same formula product* has borne the brand name "Anucort" and is called Anucort Hemorrhoidal Suppositories, as well as being sold on a private label basis to some larger customers.

Greenblatt declaration, ¶ 8 (emphasis added). Paragraph 9 of the declaration clarifies that "the same formula product" means "hemorrhoidal suppositories containing hydrocortisone acetate." Thus, G & W's grandfather clause defense rests on the same flawed premise as its "substantial evidence" argument—that Anucort has long

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[9] The records are referred to in the Declaration of Bruce E. Byer, (Plaintiff's Exhibit 8 in Support of Summary Judgment) and Plaintiff's Response to Claimant's Discovery Requests Related to the 1962 Grandfather Clause (Plaintiff's Exhibit 8 in Reply to Cliamant's Response to Motion for Summary Judgment). The court, in addressing G & W's Rule 56(f) defense, will discuss the propriety of using this information under the court's previous orders.

been recognized as safe and effective because its active ingredient has long been so recognized. As explained above, the term "drug", as used in § 321(p), refers to the product itself, not simply the product's active ingredients. *See United States v. Generix Drug Corp.*, 460 U.S. 453, 456-57 (1983). Even accepting Mr. Greenblatt's declaration, no genuine issue of fact exists as to whether the product Anucort was commercially sold prior to 1962.

Furthermore, Mr. Greenblatt's declaration fails to raise an issue as to whether Anucort is currently prescribed for use in accordance with its 1962 labeling. "Labeling" under the Act means written or printed material affixed to an article or its container, or accompanying the article. 21 U.S.C. § 321(m). The declaration fails to describe the 1962 labeling and no label is affixed as an exhibit. Under these circumstances, G & W cannot demonstrate that the current use conforms to the prior labeling. In fact, the declaration does not even allege that this condition is satisfied.

The court holds that G & W has failed to raise a genuine issue of fact under Rule 56(c) with regard to two essential elements of its grandfather clause defense.[10] G & W also argues under Rule 56(f) that G & W requires further discovery to oppose plaintiff's motion. The court disagrees, and affirms the Magistrate's order denying G & W's request for a continuance.

Rule 56(f) requires a defending party to set forth "facts essential to justify the party's opposition" upon which further discovery is needed. G & W states, with regard to the grandfather clause defense, that it "believes that other relevant information may be in the files of FDA." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 24. More specifically,

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[10] The court makes no ruling concerning the other elements.

G & W seeks discovery of "FDA's records showing the fact of G & W's manufacture of this product prior to 1962." See Reply to Plaintiff's Memorandum in Opposition to Claimant's Appeal from the Magistrate's Order, at 4.[11]

G & W's argument fails. First, plaintiff has now responded to G & W's discovery requests related to the grandfather clause. See Plaintiff's Exhibit 8 in Response. The government's response does not support G & W's position. More importantly, as discussed above, G & W's grandfather clause argument rests on a flawed legal premise—that Anucort is entitled to the defense as long as G & W marketed a product with the same active ingredient prior to 1962. Even if the FDA has documents to verify Mr. Greenblatt's contention that G & W has manufactured "hemorrhoidal suppositories containing hydrocortisone acetate" since 1958, Declaration of Carl J. Greenblatt at ¶ 9, the affirmative defense fails as a matter of law.[12] Denial of a summary judgment motion on Rule 56(f) grounds is not appropriate under these circumstances. *See Hancock Indus. v. Schaeffer*, 811 F. 2d 225, 230 (3d Cir. 1987).

The court grants plaintiff's motion for summary judgment dismissing G & W's grandfather clause defense.

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[11] The affidavit or Richard S. Morey, filed with the motion for a continuance, identifies facts relating to the "substantial evidence" issue, but not the grandfather clause. ¶ 3.

[12] For this reason, the court's consideration of the affidavit of Bruce E. Beyer—despite the court's prior order of February 17, 1987—is not inappropriate. G & W contends that it needs discovery to show that prior to 1962 G & W marketed other products containing Anucort's active ingredient. Mr. Beyer's affidavit is consistent with this fact, ¶ 2(e), Mr. Greenblatt's declaration states it directly, ¶ 9, and the court accepts it as true. G & W requires no further discovery to oppose plaintiff's motion concerning this affirmative defense.

II. *Affirmative defenses seeking remand to FDA*

G & W's other two affirmative defenses seek remand to the FDA for administrative proceedings to determine whether Anucort is a new drug. The court's holding that Anucort, as a matter of law, is a new drug renders these defenses moot. G & W effectively admits this in its brief —"If the [summary judgment] motion is denied, G & W intends to move that the Court remand this case to FDA based on those affirmative defenses." Memorandum in Opposition to Plaintiff's Motion for Summary Judgment, at 26.

CONCLUSION

The court denies G & W's motion to strike portions of the declaration of Dr. C. Carnot Evans.

The court affirms the Magistrate's order dated October 16, 1986, and thereby denies G & W's motion for a continuance of plaintiff's motion for sumary judgment pending further discovery.

The court grants plaintiff's motion for summary judgment.

/s/ H. Lee Sarokin
H. LEE SAROKIN
U.S.D.J.

Date: August 24, 1987

Original to Clerk, U.S. District Court

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civil Action No. 85-5232

UNITED STATES OF AMERICA,
Plaintiff,

v.

UNDETERMINED QUANTITIES OF AN ARTICLE OF DRUG, . . .
(ANUCORT HC SUPPOSITORIES),
Defendants.

[Filed Aug. 24, 1987]

ORDER

This matter having come before the court on plaintiff's motion for summary judgment; and the claimant having moved for a continuance of plaintiff's motion pending further discovery; and the Hon. Ronald J. Hedges, U.S. Magistrate, by order dated October 16, 1986, having denied claimant's motion for a continuance; and claimant having appealed to said order to this court; and claimant having moved for an order to disregard statements in the affidavit of Dr. C. Carnot Evans; and the court having considered the written submissions and having heard oral argument on said motions; and for the reasons expressed in the accompanying opinion,

IT IS this 24th day of August, 1987, hereby

ORDERED that the Magistrate's order of October 16, 1986 is affirmed and thereby claimant's motion for a

continuance of plaintiff's motion for summary judgment is denied, and it is further

ORDERED that claimant's motion to disregard statements in the affidavit of Dr. Evans is denied, and it is further

ORDERED that plaintiff's motion for summary judgment is granted

/s/ H. Lee Sarokin
H. LEE SAROKIN
U.S.D.J.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 88-5030

UNITED STATES OF AMERICA,

v.

UNDETERMINED QUANTITIES OF A DRUG, ANUCORT HC SUPPOSITORIES CONTAINING HYDROCORTISONE ACETATE in any size container in the possession of G&W LABORATORIES, INC., SOUTH PLAINFIELD, NEW JERSEY, labeled in part: (foil strip) "* * * HEMORRHOIDAL-HC SUPP. 0152 * * *"

G & W LABORATORIES, INC., CLAIMANT,
Appellant

(D.C. Civil No. 85-5232)

SUR PETITION FOR PANEL REHEARING

Present: HIGGINBOTHAM, BECKER, and GREENBERG, *Circuit Judges*

The petition for rehearing filed by appellant G & W Laboratories, Inc., having been submitted to the judges who participated in the decision of this court and no judge who concurred in the decision having asked for rehearing, the petition for panel rehearing is DENIED.

BY THE COURT:

/s/ [Illegible]
Circuit Judge

Dated: Sep. 7, 1988

APPENDIX D

21 U.S.C.A. § 321(p) (West 1972):

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

APPENDIX E

21 U.S.C.A. § 355(d) (West 1972):

Grounds for refusing application; approval of application; "substantial evidence" defined

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that

clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.



APPENDIX F

21 C.F.R. § 320.22 (1988):

§ 320.22 Criteria for waiver of evidence of in vivo bioavailability.

(a) Any person submitting a full or abbreviated new drug application, or a supplemental application proposing any of the changes set forth in § 320.21(b), may request the Food and Drug Administration to waive the requirement for the submission of evidence demonstrating the in vivo bioavailability of the drug product that is the subject of the application. A request for waiver shall be submitted with the application. The Food and Drug Administration shall waive the requirement for the submission of evidence of in vivo bioavailability if the drug product meets any of the provisions of paragraph (b), (c), or (d) of this section.

(b) For certain drug products the in vivo bioavailability of the drug product may be self evident or not necessary for the product to achieve any of its intended purposes. The Food and Drug Administration shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the product meets one of the following criteria:

(1) The drug product meets both of the following conditions:

(i) It is a solution intended solely for intravenous administration.

(ii) It contains an active drug ingredient or therapeutic moiety in the same solvent and concentration as an intravenous solution that is the subject of an approved full new drug application.

(2) The drug product is a topically applied preparation, e.g., a cream, ointment, or gel, intended for local therapeutic effect.

(3) The drug product is an oral dosage form that is not intended to be absorbed, e.g., an antacid or a radiopaque medium.

(4) The drug product meets both of the following conditions:

(i) It is administered by inhalation as a gas or vapor, e.g., a medicinal or an inhalation anesthetic.

(ii) It contains an active drug ingredient or therapeutic moiety in the same dosage form as a drug product that is the subject of an approved full new drug application.

(5) The drug product meets all of the following conditions:

(i) It is an oral solution, elixir, syrup, tincture, or similar other solubilized form.

(ii) It contains an active drug ingredient or therapeutic moiety in the same concentration as a drug product that is the subject of an approved full new drug application.

(iii) It contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

* * * *

APPENDIX G

53 FED. REG. 30776 (August 15, 1988):

* * * *

While it is not clear whether the Panel intended testing of all products, including formulations containing Category I ingredients, FDA agrees with the comments that final formulation testing should not be required for anorectal drug products because the products are topically applied and because, to date, there has been no demonstrated bioavailability problem with any of the products at issue. The in vivo waiver provision of § 320.22 (b) (2) for topically applied products reflects the fact that certain topically applied products, that are applied directly to the site of drug action, are less prone to bioavailability problems than are some other drugs and, accordingly, their bioavailability may, in some instances, be determined by means other than in vivo product testing. With regard to the products subject to this monograph, FDA will not require in vivo bioavailability testing, but will address product bioavailability in the context of the monograph requirements of (1) appropriate vehicles and other inactive infredients and (2) compliance with appropriate good manufacturing practices.

Accordingly, the agency will not require final formulation testing of anorectal drug products covered by a final monograph. Category I anorectal active ingredients may be formulated in appropriate vehicles without additional testing, provided the product is manufactured according to the regulations for the Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211). Manufacturers should be aware that the newness of a dosage, or method * * * of administration or application, or other condition of use * * * may affect the "newness" of a drug. (See 21 CFR 310.(h) (5).)

* * * *